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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,298	BERGMANN ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *12-14,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,15 and 16* is/are rejected.

7)☒ Claim(s) *2-11,15 and 16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/24/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of **cardiac disease** as the species of disease in the reply filed on 1/2/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 12-14 and 17-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 1/2/08.

Information Disclosure Statement

3. The information disclosure statement filed 7/24/06 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. **Specifically, the reference by Ueda et al. (Cite No. DO on page 2 of the IDS) was not considered because a copy of the reference was not provided.**

Specification

4. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

Claim 11 recites that "wherein the labeling system comprises rare earth cryptates or chelates in combination with a fluorescent or chemiluminescent dye, in particular of the cyanine type". Antecedent basis could not be found in the specification for "rare earth cryptates", "chelates" or "cyanine type" dyes.

5. The disclosure is objected to because of the following informalities:

6. The word "chemiluminescent" is misspelled on page 17, line 1.

7. The heading "The Brief Description of the Drawings" is not present in the specification. A reference to and brief description of the drawing(s) is required as set forth in 37 CFR 1.74. See MPEP § 608.01(f).

Claim Objections

8. Claims 2-11 and 15-16 are objected to because of the following informalities:

9. Dependent claims 2-11 and 15-16 recite "Method according to claim" X. The language "The method of claim" X is suggested in order to avoid ambiguity.

10. Claim 3 recites a "SPALT" assay. It is suggested that in the first instance of an abbreviation in the claims that the abbreviation be accompanied by the full term.

11. Claim 4 should apparently read that --the biological fluid is plasma-- in lines 2-3.

12. Claim 11 is objected to because it refers to "a fluorescent or chemiluminescent dye, in particular of the cyanine type". The exemplary language "in particular" is objected to because it may lead to confusion over the intended scope of a claim. The Examiner suggests rewording the claim for clarity.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1-11 and 15-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

15. Claim 1 recites a method in which "a mid-regional partial peptide (SEQ ID NO:3) of proadrenomedullin which comprises amino acids 45-92 of the complete preproadrenomedullin sequence (SEQ ID NO:1) is measured. The claim is indefinite because the designation "SEQ ID NO:3" implies that SEQ ID NO:3 per se is detected (i.e., the 48 amino acid peptide consisting of SEQ ID NO:3). However, the claim also recites that the partial peptide that is measured "comprises" amino acids 45-92, which would read on not only SEQ ID NO:3 but also peptides that have this sequence plus additional amino acids on either end. Accordingly, the scope of the claim is unclear because it is not clear whether the method detects SEQ ID NO:3 or alternatively SEQ ID NO:3 and any peptide that comprises SEQ ID NO:3.

16. Claim 2 recites the limitation "the mid-pro-AM" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim. For the purposes of examination, the reference was assumed to refer back to "the mid-regional partial peptide (SEQ ID NO:3)" recited in claim 1.

17. Claim 3 recites the limitation "the analyte" in line 2. There is insufficient antecedent basis for this limitation in the claim.

18. Claim 6 recites the limitation "the antibodies" in line 2. There is insufficient antecedent basis for this limitation in the claim since claim 3 refers to both "a labeled antibody" as well as to "at least two antibodies" which are used in a SPALT and a sandwich assay, respectively. Therefore, there is ambiguity as to which antibodies (and which assay) are being invoked in claim 6.

19. Similarly, claim 7 refers to "both antibodies", which is ambiguous since at least three antibodies are recited in claim 3.

20. Similarly, claims 8 and 8 refer to "one of the antibodies" and to "the other" antibody, which is ambiguous for the reasons discussed above.

21. Claim 9 recites that the other antibody "can be" bound selectively to a solid phase, which renders the claim indefinite because it is not a positive recitation. It is unclear whether the antibody is actually bound to the solid phase or not.

22. Claim 10 recites the limitations "the liquid reaction mixture", "the second labeling component", "the first antibody", and "the second antibody", "the resulting sandwich complexes", and "the measuring solution". There is insufficient antecedent basis for these limitations in the claim.

23. Claim 11 recites a dye "of the cyanine type". This terminology renders the claim indefinite because the specification does not clearly define or otherwise exemplify what dyes would be considered cyanine "type" dyes. Although cyanine dyes *per se* are known in the art, absent a disclosed standard one skilled in the art would not know how similar a given dye could be to a cyanine dye (in structure, reactivity, color, etc.) while still falling within the scope of the claim.

Claim Rejections - 35 USC § 102

24. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

25. Claims 1 and 15-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Bergmann et al. (WO 00/22439, Applicant's IDS of 7/24/06).

The citations below refer to the text of the Bergmann et al. publication, which is in German. However, it is noted that a translation of the document is available by way of the U.S. counterpart (US 6,756,483 B1, also of record).

Bergmann et al. teach determination of pro-adrenomedullin 45-92 using a commercially available RIA kit. See pages 17-19, section D.2. This prohormone is the same as the "mid-

regional partial peptide of proadrenomedullin" claimed instantly, as made clear by the reference to amino acids 45-92. Bergmann et al. teach determining pro-adrenomedullin 45-92 in the serum of normal subjects and those suffering from sepsis; elevated levels were seen in the sepsis patients (see also Figure 7 and the accompanying legend on page 8; and Table 3).

With respect to the recitation in claim 1 that the level of the mid-regional partial peptide is indicative of the level of adrenomedullin, such a statement may be interpreted as simply a descriptive statement characterizing the results of the method steps earlier recited and/or referring to inherent properties of the peptide. Therefore, the "wherein" statement is not found to impart further patentable weight to the claim. See MPEP 2111.04.

With respect to claim 15, which recites that the adrenomedullin determination is "used in the area of cardiac diagnosis", it is noted that the claim does not clearly call for any additional active method steps to be performed. As such, the claim can be interpreted as simply referring to a possible intended downstream use of the method of claim 1 and does not impart patentable weight.

With respect to claim 16, Bergmann et al. also determined pro-ANP or pro-ANF and pro-BNP in parallel (page 17, first paragraph and Table 3), which are disclosed in the instant specification as cardiac parameters (page 18).

26. Claims 1-4, 6-10, and 15-16 are rejected under 35 U.S.C. 102(e) as being anticipated by Bougueleret et al. (US 2007/0082363 A1, of record).

Bougueleret et al. teach diagnosis of cardiovascular disorders by detecting and/or quantifying SEQ ID NO:3 ("CPP 19") and other so-called "cardiovascular disorder plasma

polypeptides" or CPPs) (see especially claims 1-5 and paragraphs 12-14, 28, 35, 63-68, 140-161, 168-212). SEQ ID NO:3 as taught by Bougueleret et al. is identical to instant SEQ ID NO:3 (see Figure 1 of the reference and the Examiner's sequence search results via SCORE).

With respect to claims 2-3, Bougueleret et al. teach sandwich or "double determinant" ELISA assays that use two antibodies, one of which is labeled directly or indirectly (paragraph 177 on page 27).

With respect to claim 4, the reference teaches assaying SEQ ID NO:3 in plasma (see, e.g., paragraphs 35, 207, and claim 5).

With respect to claims 6-7, the reference teaches both polyclonal and monoclonal antibodies [0154], [0157]; the former may be purified by immunoaffinity chromatography [0155].

With respect to claim 8, Bougueleret et al. teach that anti-CPP antibodies may be made by immunizing mammals with the CPP or a fusion protein thereof [0154], [0157], i.e., in this case CPP 19 or SEQ ID NO:3. Since the claim employs open transitional language to indicate that the eliciting antigen "comprises" amino acids 68-86 or 83-94 of pre-proAM, this would encompass antibodies raised against an antigen that is SEQ ID NO:3 *per se* as in Bougueleret et al.

Although Bougueleret et al. do not specifically mention that the CPP protein used to raise antibodies is "synthetic", it is noted that the claim does not require that the indicated steps actually be performed in the method. Rather, the limitations as to specific synthetic peptide sequences convey product-by-process limitations relating to the process by which the antibodies used in the detection method are made. Applicant is reminded that the patentability of a product

does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Considering the structure implied by the process steps recited, no structural differences are disclosed or apparent in the resulting antibodies through the use of a synthetic SEQ ID NO:3 vs. that obtained by other means.

Therefore, although the reference is silent as to the specific synthetic sequences recited in instant claim 8, since the recited process reads on producing antibodies against SEQ ID NO:3 *per se*, and because no structural differences are apparent through the use of "synthetic" eliciting antigens, the teachings of Bougueleret et al. read on the claim since the prior art process for producing antibodies is indistinguishable from that recited.

With respect to claim 9, the double determinant ELISA discussed above involves coating the non-labeled antibody on a solid support (paragraph 177 on page 27).

With respect to claim 10, the double determinant ELISA involves a solid support bound to the first antibody (i.e., first labeling component) and a label such as peroxidase (i.e., second labeling component) bound to the second antibody.

With respect to claim 16, the reference teaches determining SEQ ID NO:3 in combination with other cardiovascular disorder plasma polypeptides or CPPs [0213].

Claim Rejections - 35 USC § 103

27. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

28. Claims 2-3 and 5-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bergmann et al. in view of Harlow & Lane (Harlow, E. and Lane, D., Antibodies: A Laboratory Manual (1988) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pages 53, 60-61, 72-76, and 578-579).

Bergmann et al. is as discussed above, which teaches determination of pro-adrenomedullin 45-92 (i.e., SEQ ID NO:3) using a commercially available radioimmunoassay (RIA) kit. However, the reference does not provide details relating to this kit and therefore fails to specifically teach or suggest an immunoassay involving at least one labeled antibody that specifically recognizes a sequence of mid-proAM. Regarding claim 5, the reference also fails to teach or suggest using multiple antibodies that bind to the region from amino acids 60-90. Regarding claim 8, the reference is silent as to the specific process of producing the antibodies.

Harlow & Lane teach laboratory procedures involving antibodies, including immunoassays. For example, the reference teaches that one of the most useful immunoassays is the two-antibody sandwich technique, which can be used to determine antigen concentration in a quick and accurate manner (pages 578-579). Such sandwich immunoassays require two antibodies that bind to non-overlapping epitopes on the antigen; either two monoclonal antibodies or one batch of affinity-purified polyclonal antibodies can be used (ibid). The first

antibody is bound to a solid phase, while the second antibody is labeled (see diagram on the bottom of page 578, and page 579).

Therefore, with respect to claims 2-3 and 9, it would have been obvious to arrive at the claimed invention by substituting the sandwich immunoassay format of Harlow & Lane for the radioimmunoassay in the method of detecting pro-adrenomedullin 45-92 of Bergmann et al. It would have been further obvious to select either monoclonal or affinity-purified polyclonal antibodies for such a sandwich immunoassay (as in claims 6-7) since Harlow & Lane teach that both of these produce excellent signal strength and specificity (page 578).

One would be motivated to use the sandwich immunoassay format of Harlow & Lane in the method of Bergmann et al. in order to achieve the same purpose, namely determination of pro-adrenomedullin 45-92. One would also be motivated to do this in light of the teachings of Harlow & Lane that sandwich immunoassays are one of the most useful immunoassays, being quick and accurate. One would also be modify the teachings of Bergmann in this manner so as to avoid working with radioactive materials, which are necessary in the RIA kit exemplified by the reference.

With respect to claim 5, Harlow & Lane further teach that in addition to pure antigens, it was also known to use synthetic peptides as immunogens in order to raise antibodies (pages 53 and 72-76). This is advantageous in that anti-peptide antibodies can be prepared immediately, and particular regions of a protein can be targeted specifically for antibody production (page 73, first full paragraph and the box at the bottom of pages 72-73). The reference further teaches suggestions for designing peptides that will recognize the native protein (page 75). For example, the reference teaches that several workers have noted that carboxy-terminal sequences are often

exposed and can be targeted for anti-peptide sequences (page 75, "Choosing the Appropriate Peptide Sequence").

It is noted that amino acids 60-94 correspond to the C-terminal region of SEQ ID NO:3. Therefore, it would have been obvious to arrive at the invention of claim 5 by raising antibodies against peptides corresponding to carboxy-terminal sequences of SEQ ID NO:3 according to recommended laboratory procedures for producing antibodies as taught by Harlow & Lane. One would have had a reasonable expectation of success because Harlow & Lane teach that a surprisingly high percentage of antibodies raised using carboxy-terminal sequences will recognize the native protein.

With respect to claim 8, as discussed further above the claimed method does not actually require that the indicated steps be performed. Rather, the limitations as to specific synthetic peptide sequences convey product-by-process limitations relating to the process by which the antibodies used in detection are made. Considering the structure implied by the process steps recited, it is noted that the claim employs open transitional language to indicate that the eliciting antigen "comprises" amino acids 68-86 or 83-94 of pre-proAM. Since the claim language is open, this would encompass antibodies raised against SEQ ID NO:3 *per se*.

In addition to antibodies raised against synthetic peptides, Harlow & Lane also teach that pure antigens or bacterially-expressed proteins can be used to raise antibodies (see pages 60-61 and the box on the bottom of pages 72-73). Harlow & Lane teach that when a cloned DNA sequence is available, antibodies can be prepared using either of these approaches, which each have advantages and disadvantages (box at bottom of page 72). When feasible, both approaches should be used.

Therefore, it would have been further obvious to arrive at the claimed invention by raising antibodies against either SEQ ID NO:3, either as pure antigen or in bacterially-expressed form. Since SEQ ID NO:3 *per se* "comprises" amino acids 68-86 and 83-92 of pre-proAM, antibodies raised against full-length SEQ ID NO:3 (either as pure antigen or as a bacterially-expressed protein) would read on the recited process. Although the reference does not mention that such forms are "synthetic", as discussed above no structural differences are seen with regards to this specific method of production.

Motivation to do this comes from the teachings of Harlow & Lane that it is routine in the art to raise antibodies against pure antigen, synthetic peptides, and/or bacterially expressed proteins. Additional motivation comes from the teachings of Harlow & Lane that where feasible, both anti-peptide and anti-bacterially expressed protein antibodies should be attempted.

29. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bergmann et al. in view of Hrubec et al. ("Plasma Versus Serum: Specific Differences in Biochemical Analyte Values" Journal of Avian Medicine and Surgery 16(2):101-105, 2002).

Bergmann et al. is as discussed above, which teaches determination of pro-adrenomedullin 45-92 (i.e., SEQ ID NO:3) in *serum* (see section D.2), but which fails to specifically teach determination in *plasma*.

Hrubec et al. teach that biochemical analysis can be conducted using either plasma or serum, and that these are similar sample types (p. 101, right column). In their experiments, the authors noted differences in analyte levels when measured in plasma vs. serum (abstract). The reference teaches that such differences are artifactual and may prevent accurate diagnosis of

disease states or other physiologic conditions (page 104, right column, last paragraph). To avoid this potential problem, Hrubec et al. recommend that blood chemistry values be determined from plasma.

Therefore, it would have been obvious to one of ordinary skill in the art to detect pro-adrenomedullin 45-92 (i.e., SEQ ID NO:3) in plasma rather than in serum in the method of Bergmann et al. One would be motivated to do this in light of the teachings of Hrubec et al. that plasma and serum are similar samples and that biochemical analysis can be conducted using either. Furthermore, one would be motivated to use plasma rather than serum as recommended by Hrubec et al. so as to avoid artifactual differences that may arise in serum that may prevent accurate diagnosis of disease states.

30. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bougueleret et al. in view of Harlow & Lane.

The references are as discussed above. Bougueleret et al. teaches sandwich or "double determinant" ELISA methods to detect SEQ ID NO:3, but fails to specifically teach that the two antibodies used in the assay bind to a region of the peptide that extends from amino acid 60 to amino acid 90 of pre-proAM. However, as discussed above, this region corresponds to the C-terminal region of SEQ ID NO:3.

Therefore, in light of the teachings of Harlow & Lane that is routine in the art to use synthetic peptides as immunogens in order to raise antibodies, and that carboxy-terminal sequences are suggested for designing such peptides since they are likely to be immunogenic, it would have been obvious to arrive at the claimed invention by designing peptides corresponding

to carboxy-terminal sequences of SEQ ID NO:3 and raising antibodies against such peptides. One would have had a reasonable expectation of success because Harlow & Lane teach that a surprisingly high percentage of antibodies raised using carboxy-terminal sequences will recognize the native protein.

31. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bougueleret et al. in view of Mathis et al. ("Probing Molecular Interactions with Homogeneous Techniques Based on Rare Earth Cryptates and Fluorescence Energy Transfer" Clin. Chem. 41/9, 1391-1397 (1995)).

Bougueleret et al. is as discussed above, which teaches diagnosis of cardiovascular disorders by detecting and/or quantifying SEQ ID NO:3 ("CPP 19"). Bougueleret et al. teach detection via sandwich or "double determinant" ELISA assays that use two antigen-specific antibodies, one of which is labeled directly or indirectly (paragraph 177 on page 27).

The teachings of Bougueleret et al. differ from the instantly claimed invention in that the reference fails to specifically teach that the labeling system comprises rare earth cryptates or chelates in combination with a fluorescent or chemiluminescent dye.

Mathis et al. teach homogeneous immunoassay methods based on the use of rare earth cryptates as fluorescent labels (the abstract and page 1392). Such immunoassays involve two monoclonal antibodies raised against the antigen, which are labeled respectively with Eu^{3+} cryptate (rare earth cryptate) and with allophycocyanin (cyanine type fluorescent dye). See page 1392 and Figure 1 in particular.

Mathis et al. further teach that such homogeneous fluoroassays are free from media interactions, allowing for development of assays that involve only a minimal perturbation of equilibrium or steric environment (page 1395, "Discussion" to page 1396, left column).

Therefore, it would have been obvious to one of ordinary skill in the art to modify the double determinant ELISA assay of Bougueleret et al. so as to use the rare earth cryptate labeling system of Mathis et al. In particular, it would have been obvious to label one of the antibodies in the sandwich assay of Bougueleret et al. with Eu^{3+} cryptate and the other with allophycocyanin as taught by Mathis et al. in order to detect SEQ ID NO:3 in a homogeneous sandwich assay. Put another way, it would have been obvious to use the homogeneous sandwich fluoroassay of Mathis et al. in order to detect SEQ ID NO:3 in the method of diagnosing cardiovascular disease of Bougueleret et al.

One would be motivated to do this in light of the teachings of Mathis et al. that the use of rare earth cryptates as fluorescent labels in immunoassays allows for homogeneous assays (i.e., no separation steps). Therefore, one would be motivated to perform a sandwich immunoassay for SEQ ID NO:3 using the labels of Mathis et al. so as to eliminate the need for separation or wash steps needed for typical ELISA procedures (such as that of Bougueleret et al.). Furthermore, one would have been motivated to detect SEQ ID NO:3 by the homogeneous fluoroassay of Mathis et al. in order to allow for an assay that is free from media interactions.

One would have had a reasonable expectation of success because Mathis et al. also teaches that labeling of different types of molecules was done with ease (page 1395, "Discussion").

32. Claims 2-3, 6, and 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bergmann et al. in view of Mathis et al.

The references are as discussed above. Bergmann et al. teaches determination of pro-adrenomedullin 45-92 by radioimmunoassay. However, the references fail to specifically teach sandwich immunoassays, including those that use a labeling system that comprises rare earth cryptates or chelates in combination with a fluorescent or chemiluminescent dye.

The teachings of Mathis et al. are as discussed in detail above. Mathis et al. teach a sandwich or two-antibody immunoassay in which one of the antibodies is labeled with Eu^{3+} cryptate and the other with allophycocyanin. Such labels form a donor-acceptor pair that can participate in nonradiative energy transfer when the labels are brought together in close proximity via interaction with the target antigen (see especially Figure 1). This allows for a homogeneous assay to be conducted (i.e., no separation steps).

Therefore, it would have been obvious to one of ordinary skill in the art to detect pro-adrenomedullin 45-92 by the fluoroimmunoassay of Mathis et al. in the method of Bergmann et al. instead of by radioimmunoassay. In particular, it would have been obvious to use two monoclonal antibodies against the antigen (i.e., pro-adrenomedullin 45-92) and to label one of the antibodies with Eu^{3+} cryptate (i.e., rare earth cryptate) and the other with allophycocyanin (i.e., fluorescent cyanine-type dye). Put another way, it would have been obvious to use the homogeneous sandwich fluoroassay of Mathis et al. in order to detect pro-adrenomedullin 45-92 in the method of Bergmann et al. One would be motivated to do this in order to detect pro-adrenomedullin 45-92 in a homogeneous assay, requiring no separation steps. One would also be

motivated to use the Mathis et al. fluoroimmunoassay in order to avoid the need to use radioactive labels which were used in the RIA kit of Bergmann et al.

One would have had a reasonable expectation of success because Mathis et al. also teaches that labeling of different types of molecules was done with ease (page 1395, "Discussion").

Double Patenting

33. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

34. Claims 1 and 15-16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 11/997250. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '250 application also claims a method of detecting the concentration of the midregional proadrenomedullin partial peptide having amino acids 45-92 of

preproadrenomedullin in biological fluids (see especially claims 1 and 3). The peptide may be measured by sandwich immunoassay (see claim 4), may be measured in plasma (see claim 11), and other parameters may be measured as part of a multi-parameter determination (see claims 7-10). Although instant claims 15-16 recite that the determination of adrenomedullin is used in the area of cardiac diagnosis, while the copending application relates to neurodegenerative disorders, as discussed above the instant claims do not clearly require that any additional active method steps be performed. Therefore, the claims of the copending application, in which the adrenomedullin partial peptide having amino acids 45-92 of preproadrenomedullin is measured in a biological fluid, read on the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

35. Claims 1 and 15-16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of copending Application No. 11/937061. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '061 application also claims a method of determining the level of pro-adrenomedullin or partial peptides or fragments thereof for *in vitro* diagnosis of patients post-myocardial infarction (see claim 1). The peptide fragment may be MR-proADM (see claim 2), which is the same peptide as the instantly recited SEQ ID NO:3 (see the specification of the '061 application at [006], which defines "MR-proADM as the peptide comprising amino acids 45-92 of preproADM). The '061 application also claims that additional markers can also be determined (i.e., multi-parameter determination). See claims 4-15.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

36. Claims 2-9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 11/997250 in view of Harlow & Lane, or in the alternative as being unpatentable over claims 1-17 of copending Application No. 11/937061.

The '061 application fails to specifically recite that MR-proADM is detected by sandwich immunoassay. The '250 application recites a sandwich immunoassay (claim 4), but does not specifically mention that the assay uses a labeled analyte-specific antibody. The copending applications also fail to specifically recite that the antibodies for the sandwich immunoassay bind to a region on mid-proAM that extends from amino acids 60-94 of pre-proAM, or that the antibodies are obtained by immunization with the synthetic peptides recited in claim 8.

The teachings of Harlow & Lane are discussed in detail above.

Regarding claims 2-3 and 9, it would have been obvious to arrive at the claimed invention by employing the sandwich immunoassay format of Harlow & Lane to detect MR-proADM in the methods of the '061 or '250 applications. One would also be motivated to do this in light of the teachings of Harlow & Lane that sandwich immunoassays are one of the most useful immunoassays, being quick and accurate.

It would have been further obvious to select either monoclonal or affinity-purified polyclonal antibodies for such a sandwich immunoassay (as in claims 6-7) since Harlow & Lane teach that both of these produce excellent signal strength and specificity.

Regarding claim 5, in light of the teachings of Harlow & Lane discussed in detail above, it would have been obvious to arrive at the claimed invention by raising antibodies against C-terminal sequences of SEQ ID NO:3, since amino acids 60-94 correspond to the C-terminus of SEQ ID NO:3. It would have been obvious to do this according to routine laboratory procedures which suggest C-terminal sequences as being likely to produce antibodies that recognize the native protein.

Regarding claim 8, Harlow & Lane also teach that pure antigens or bacterially-expressed proteins can be used to raise antibodies as detailed above. Therefore, it would have been further obvious to arrive at the claimed invention by produce the antibodies for the sandwich immunoassays using either SEQ ID NO:3, either as pure antigen or in bacterially-expressed form. Since SEQ ID NO:3 *per se* "comprises" amino acids 68-86 and 83-92 of pre-proAM, antibodies raised against full-length SEQ ID NO:3 (either as pure antigen or as a bacterially-expressed protein) would read on the recited process.

Motivation to do this comes from the teachings of Harlow & Lane that it is routine in the art to raise antibodies against pure antigen, synthetic peptides, or bacterially expressed proteins.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

37. Claims 2-3, 6, and 10-11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 11/997250 in view of Mathis et al., or in the alternative as being unpatentable over claims 1-17 of copending Application No. 11/937061 in view of Mathis et al.

The '061 application fails to specifically recite that MR-proADM is detected by sandwich immunoassay. The '250 application recites a sandwich immunoassay (claim 4), but does not specifically mention that the assay uses a labeled antibody. The copending applications also fail to recite an immunoassay that involves a labeling system that comprises rare earth cryptates or chelates in combination with a fluorescent or chemiluminescent dye.

In light of the Mathis et al. discussed in detail above, it would have been obvious to one of ordinary skill in the art to detect pro-adrenomedullin 45-92 (MR-proADM, SEQ ID NO:3) in the methods of the copending applications by the fluoroimmunoassay of Mathis et al. in the method of Bergmann et al. In particular, it would have been obvious to use two monoclonal antibodies against the antigen (i.e., pro-adrenomedullin 45-92) and to label one of the antibodies with Eu^{3+} cryptate (i.e., rare earth cryptate) and the other with allophycocyanin (i.e., fluorescent cyanine-type dye). Put another way, it would have been obvious to use the homogeneous sandwich fluoroassay of Mathis et al. in order to detect MR-proADM in the methods of the '250 or '061 applications. One would be motivated to do this in order to detect pro-adrenomedullin 45-92 in a homogeneous assay, requiring no separation steps. One would also be motivated to use the Mathis et al. fluoroimmunoassay in order to avoid the need to use radioactive labels.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

38. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

39. Bridon et al. (US 6,849,714 B1) and (US 6,887,470) teach SEQ ID NO:939, which is identical to instant SEQ ID NO:3 (see, e.g., US 6,847,714 at column 22, lines 47-57.

40. Enomoto et al. ("High throughput screening for human interferon-gamma production inhibitor using homogenous time-resolved fluorescence" J Biomol Screen. 2000 Aug;5(4):263-8) also teach homogeneous immunoassays similar to taught by Mathis et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641

/Long V Le/
Supervisory Patent Examiner, Art Unit 1641